REMARKS/ARGUMENTS

The Present Invention

The present invention is directed to a composition comprising a dual specificity T lymphocyte comprising a recombinant chimeric receptor or recombinant T cell receptor, which is reactive with a tumor antigen, and an endogenous T cell receptor reactive with a cell that is allogeneic to the T lymphocyte, and the cell that is allogeneic to the T lymphocyte. The present invention is also directed to other related compositions and a method of preparing lymphocytes having dual specificity.

The Pending Claims

Claims 1, 4, 7, 8, 10, 40, 41, 44-46, 52-61, 71-76, and 79-93 are pending.

The Office Action

The Office Action points out that the Information Disclosure Statement (IDS) submitted on August 25, 2005, allegedly does not comply with 37 CFR 1.97, because the publication dates of each GenBank Accession record listed therein are not provided. The Office Action also objects to the specification for not having up-to-date information on U.S. Application No. 08/547,263, which is cited in paragraph 0052 on page 17.

The Office Action maintains the rejection of claims 1, 7, 40, 41, 71, 72, 79-83, 92, and 93 under 102 (b) as allegedly anticipated in view of Altenschmidt et al., *J Immunol* 159: 5509-5515 (1997) (hereinafter "Altenschmidt") and of claims 1, 7, 40, 45, 52, 61, 71, 72, 76, 79-83, 87, and 91-93 under 102 (b) as allegedly anticipated by Beecham et al., *J Immunother* 23: 332-343 (2000) (hereinafter "Beecham"). The Office Action further maintains the rejection of claims 1, 7, 8, 40, 41, 45, 46, 52, 56, 58, 61, 71, 72, 75, 76, 79-83, 86, 87, and 90-93 under 103 (a) as allegedly unpatentable in view of Beecham in view of Terheyden et al., *J Immunol* 164: 6633-6639 (2000) (hereinafter "Terheyden") and Münz et al., *J Immunol* 162: 25-34 (1999) (hereinafter "Münz"). Also, the Office Action maintains the rejection of claims 4, 10, 44, 53-55, 57, 59, 60, 73, 74, 84, 85, 88, and 89 under 103 (a) as allegedly unpatentable in view of Beecham in view of Terheyden, Münz, and U.S. Patent 5,830,755 (hereinafter "the '755 patent").

Discussion of the Information Disclosure Statement

Applicants submit herewith an Information Disclosure Statement, which is the same as that previously submitted on August 25, 2005, with the publication dates of the GenBank Accession records noted. The full consideration of the references listed in the attached Form 1449 by the Examiner is hereby respectfully requested.

Discussion of the Specification

The specification of the instant application has been amended to recite the publication number of U.S. Application No. 08/547,263 in paragraph 0052 on page 17. In view of the amendment, the status of the application no longer needs to be updated.

Discussion of the Anticipation Rejections

A. Altenschmidt

According to the Office Action, Altenschmidt anticipates claims 1, 7, 40, 41, 71, 72, 79-83, 92, and 93, because the reference allegedly discloses a composition comprising T lymphocytes comprising a chimeric receptor having antigen specificity for a tumor antigen (Erb-B2 receptor) and an endogenous T cell receptor which has antigenic specificity for an allogeneic cell, wherein the allogeneic cell is either an HC11 or HC11 R2 target cell. The Office Action specifically contends that the property of having an endogenous T cell receptor reactive with an allogeneic cell is an intrinsic property of all T lymphocytes.

The rejection in view of Altenschmidt is improper, because Altenschmidt does not disclose each and every limitation of the claims. Specifically, the T lymphocytes of Altenschmidt do not comprise an endogenous T cell receptor which has antigenic specificity for either HC11 or HC11 R2 target cells. This is evidenced by the data shown in Figure 4 of Altenschmidt. Figure 4 demonstrates that the T lymphocytes expressing the chimeric receptor are reactive to the target cells *only* when (1) the T lymphocytes are expressing the chimeric receptor reactive with Erb-B2 receptor and (2) the target cells are expressing the Erb-B2 receptor. If the T lymphocytes of Altenschmidt comprised an endogenous T cell receptor reactive to HC11 or HC11 R2 target cells, the T lymphocytes would have reacted with the target cells, by way of lysing the target cells, in a manner independent of the

expression of the Erb-B2 receptor and of the chimeric receptor. That is to say that the T lymphocytes would have reacted with HC11 or HC11 R2 cells through the endogenous T cell receptor. That was not the case, however. Therefore, the Office Action's assertion that the property of having an endogenous T cell receptor reactive with an allogeneic cell is an intrinsic property of all T lymphocytes is false.

In view of the foregoing, Altenschmidt does not disclose each and every limitation of the claim. Applicants, therefore, request that the rejection be withdrawn.

B. Beecham

According to the Office Action, Beecham anticipates claims 1, 7, 40, 45, 52, 61, 71, 72, 76, 79-83, 87, and 91-93 under 102 (b), because Beecham allegedly discloses a composition comprising (1) a population of human T lymphocytes transduced with a chimeric receptor reactive with the tumor antigen CEA and (2) tumor cell cultures, which are allogeneic to the T lymphocytes.

As a first matter, Beecham has a publication date of May-June 2000 (see citation of Beecham from PubMed database attached hereto). Since the instant application was filed on March 9, 2001, Beecham is not prior art under 35 USC 102(b). The rejection in view of Beecham is improper on this basis alone.

In the instance that the Office takes the new position that Beecham is prior art under 35 USC 102(a), Applicants traverse this rejection by providing a Declaration under 37 CFR 1.131 of Patrick Hwu (attached hereto). As evidenced by the Declaration, the instant invention was conceived of and reduced to practice by the inventors prior to May 1, 2000, i.e., prior to the the publication date of Beecham, whatever that publication date was. While the exact publication date of Beecham has not been established, since the citation refers to "May-June 2000" even assuming arguendo the publication date is May 1, 2000, the attached Declaration under 37 CFR 1.131 shows invention prior to May 1, 2000. In view of the Declaration, a 102(a) rejection in view of Beecham is moot.

The rejection in view of Beecham is furthermore improper, because Beecham does not disclose each and every limitation of the claims. Specifically, the T lymphocytes of Beecham, which lymphocytes express the chimeric receptor reactive with the tumor antigen

CEA, do not further comprise an endogenous T cell receptor which is reactive with an allogeneic cell. The Office Action claims that the property of having an endogenous T cell receptor which is reactive with an allogeneic cell is an intrisinc property of all T lymphocytes. The Office asserts that the non-specific killing of the T lymphocytes of Beecham "*might* just evidence the act of the endogenous T cell receptor reactive with a cell that is allogeneic to the T lymphocyte" (page 5 of the Office Action, emphasis added). Inherency, however may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264 (Fed. Cir. 1991)

In fact, the non-specific killing exhibited by the T lymphocytes of Beecham was explained by the authors as toxicity mediated by T-LAK cells, which are able to lyse a wide spectrum of tumor targets. See page 341, 2nd complete paragraph of the left hand column. The authors do not attribute the non-specific killing of the T lymphocytes to an endogenous receptor reactive with the tumor cells not expressing the tumor antigen.

Also, as explained above in the discussion of the anticipation rejection in view of Altenschmidt, the Office Action's assertion that the property of having an endogenous T cell receptor which is reactive with an allogeneic cell is an intrisinc property of all T lymphocytes cannot be true. If it were true, then the T lymphocytes of Altenschmidt would have lysed target cells in a manner independent of the expression of the ErbB2 receptor (on the target cells) and of the chimeric receptor (on the T lymphocytes). Therefore, the endogenous T cell receptor is not an intrinsic property of all T lymphocytes.

In view of the foregoing, it cannot be said that the T lymphocytes of Beecham intrinsically comprised an endogenous receptor reactive with an allogeneic cell. Therefore, Beecham does not disclose T lymphocytes that meet each and every limitation of the claims. The anticipation rejection in view of Beecham, therefore, cannot stand, and Applicants request that the rejection be withdrawn.

Discussion of the Obviousness Rejections

A. Beecham in view of Terheyden and Münz

According to the Office Action, claims 1, 7, 8, 40, 41, 45, 46, 52, 56, 58, 61, 71, 72, 75, 76, 79-83, 86, 87, and 90-93 are *prima facie* obvious in view of Beecham in view of Terheyden and Münz. Specifically, Beecham allegedly teaches a method comprising activating T lymphocytes and then transducing the lymphocytes with a chimeric receptor gene, which chimeric receptor is reactive to a tumor antigen. According to the Office Action, Beecham does not teach activating T lymphocytes by co-culturing with an allogeneic cell. Also, Beecham allegedly does not teach a composition comprising the T cell expressing a chimeric receptor and allogeneic monocytes. The Office Action contends that Terheyden cures the deficiency of Beecham by establishing that it was well known in the art to co-culture monocytic antigen presenting cells (APCs) with T lymphocytes as a routine means of activating T lymphocytes. Terheyden, according to the Office Action, does not teach *allogeneic* dendritic cells. Münz allegedly cures the deficiency of Terheyden by allegedly teaching that allogeneic stimulus, as compared to autologous stimulus, is powerful in obtaining potent CTL cells.

As the Declaration of Patrick Hwu provided herewith states that the instant invention was conceived of and reduced to practice prior to May 1, 2000, Beecham is not prior art to the instant application. The rejection on this basis alone is improper.

Even if Beecham were prior art to the instant application, which it is not, the rejection of the claims in view of Beecham in view of Terheyden and Münz is improper, because the criteria to establish a *prima facie* case of obviousness has not been met. Specifically, the teachings of Beecham, Terheyden, and Münz do not teach or suggest all of the claim limitations. As discussed above, Beecham does not disclose a T lymphocyte comprising *both* a chimeric receptor reactive with a tumor antigen *and* an endogenous T cell receptor reactive with a cell that is allogeneic to the T lymphocyte. The teachings of Terheyden and Münz do not cure this deficiency.

Also, the rejection in view of Beecham in view of Terheyden and Münz is improper, because there is no suggestion or motivation in any of the references of record or in the

knowledge generally available to one of ordinary skill in the art to modify Beecham or to combine Beecham with Terheyden and Münz, such that the invention would have been arrived at, at the time of filing the instant application. For example, Beecham teaches activating T cells with AIMV media supplemented with IL-2 and OKT3. However, there is no teaching or suggestion in Beecham to modify this aspect of the method of producing transduced T lymphocytes. Beecham does not, for example, discuss any problems with activating T lymphocytes by using AIMV media supplemented with IL-2 and OKT3. Therefore, upon reading Beecham, one of ordinary skill in the art at the time of filing the instant application would not have been motivated to activate the T lymphocytes by co-culturing the T lymphocytes with allogeneic cells, e.g., allogeneic dendritic cells. For the same reason, one of ordinary skill in the art upon reading Terheyden and/or Münz would not have been motivated to modify the teachings found therein or in Beecham so that the instant invention would have been arrived at.

The Office Action contends that one of ordinary skill in the art would have been motivated to modify the teachings of Beecham, because the method of activating the T lymphocytes prior to transducing the T lymphocytes taught by Beecham was not target antigen specific.

However, Beecham was not activating T lymphocytes for the purpose of creating target antigen specific T lymphocytes. Beecham activated T lymphocytes prior to transduction, because Beecham started with peripheral blood mononuclear cells, which is a mixed population of cells comprising T lymphocytes. The activation procedure of Beecham, specifically, the OKT3 treatment, allowed only the T lymphocytes of the mixed population to proliferate, so that the T lymphocytes outnumbered the other cells of the mixed population. Beecham states to this effect:

> Although cell types other than T cells may be transduced at this stage, these contaminating cells are not stimulated to replicate under the culture conditions used, whereas treatment with OKT3 induces rapid T cell proliferation. This selective T cell proliferation quickly leads to cultures that are virtually 100% T cell in origin and effectively eliminates the influence of any contaminating cells from subsequent assays.

See first complete paragraph of the left hand column on page 334. In this regard, one of ordinary skill in the art would not have been motivated to change the teachings of Beecham to be the same as the instant invention.

In view of the foregoing, the instant claims are patentable over Beecham in view of Terheyden and Münz. Applicants, therefore, request that the rejection be withdrawn.

B. Beecham in view of Terheyden, Münz, and the '755 patent

According to the Office Action, claims 4, 10, 44, 53-55, 57, 59, 60, 73, 74, 84, 85, 88, and 89 are unpatentable over Beecham in view of Terheyden, Münz, and the '755 patent.

As discussed above, in view of the attached Declaration of Patrick Hwu, Beecham is not prior art to the instant application. The rejection in view of Beecham in view of Terheyden, Münz, and the '755 patent is improper on this basis alone.

The rejection in view of Beecham in view of Terheyden, Münz, and the '755 patent is furthermore improper, because, as discussed above, Beecham does not disclose T lymphocytes comprising an endogenous T cell receptor reactive with a cell, which is allogeneic to the T lymphocytes. None of Terheyden, Münz, and the '755 patent cure this deficiency. In this regard, each and every limitation of the instant claims is not disclosed by the cited references. Therefore, the rejection cannot stand.

In view of the foregoing, the instantly pending claims are patentable over Beecham in view of Terheyden, Münz, and the '755 patent. Therefore, Applicants request the withdrawal of the rejections.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the

prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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1: J Immunother. 2000 May-Jun;23(3):332-43.

Dynamics of tumor cell killing by human T lymphocytes armed with an anti-carcinoembryonic antigen chimeric immunoglobulin T-cell receptor.

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Chimeric immunoglobulin T-cell receptors (IgTCR) join the antigen-binding portion of an antibody to one of the signaling chains of the TCR. A previous report described the construction and functional testing of an IgTCR gene directed against the carcinoembryonic tumor antigen (CEA). These preclinical studies showed the proper assembly and cell surface expression of anti-CEA IgTCR molecules, specific target antigen binding, and activation of T-cell effector functions. Although IgTCR-modified T cells function well in vitro, therapeutic applications in humans may be complicated by various factors, such as the availability of appropriate T-cell cytokines, high systemic levels of antagonistic soluble CEA, and antigenic diversity in tumor cell populations. The current study analyzes tumor cell killing by IgTCR-modified human T cells under conditions that more closely model those that may be encountered in persons with cancer. This analysis shows that 1) depriving IgTCR-modified T cells of interleukin-2 does not diminish anti-CEA cytotoxic T lymphocyte activity, but does eliminate killing by lymphokine-activated killer cells; 2) high levels of soluble CEA do not significantly inhibit tumor cell killing even when approximately 80% of the chimeric receptors are blocked; and 3) CEA+ tumor cells that can down-regulate cell surface CEA evade immune destruction by IgTCR-modified T cells. These results have important implications for application strategies and protocol design considerations for early clinical testing of IgTCR anti-tumor therapies.

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